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General Information

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_ab.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_22.pdf
https://yoda.yale.edu/system/files/coi_form_az.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. [NCT00638690 - COU-AA-301 - A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate \(CB7630\) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy](#)

2. [NCT00887198 - COU-AA-302 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate \(CB7630\) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer](#)
3. [NCT01695135 - ABI-PRO-3001 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate \(JNJ-212082\) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy](#)
4. [NCT02236637 - 212082PCR4001 - A Prospective Registry of Patients With a Confirmed Diagnosis of Adenocarcinoma of the Prostate Presenting With Metastatic Castrate-Resistant Prostate Cancer](#)
5. [NCT01867710 - 212082PCR2023 - A Randomized Phase 2 Study Evaluating Abiraterone Acetate With Different Steroid Regimens for Preventing Symptoms Associated With Mineralocorticoid Excess in Asymptomatic, Chemotherapy-naïve and Metastatic Castration-resistant Prostate Cancer \(mCRPC\) Patients](#)
6. [NCT01715285 - 212082PCR3011 - A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy \(ADT\) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naïve Prostate Cancer \(mHNPC\)](#)
7. [NCT01591122 - ABI-PRO-3002 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate \(JNJ-212082\) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

The Impact of Second Generation Anti-Androgens on Sexual Function in Men with Advanced Prostate Cancer

Narrative Summary:

Second generation anti-androgens have recently gained FDA approval for their ability to improve survival in men with advanced prostate cancer. However, the impact these medications have on erectile and sexual function has not been investigated. We aim to use an aggregate of existing data from clinical trials that demonstrated the efficacy of these medications to answer these questions. Men in these trials completed quality-of-life surveys regarding their erectile function and sexual satisfaction before, during, and after treatment. We aim to use this data to characterize the effect of second generation anti-androgens have on erectile and sexual function.

Scientific Abstract:

Background: Prostate cancer is the most common malignancy in men, and the second most common cause of male cancer-related death (1). In the last decade, a new generation of anti-androgen drugs have been shown to improve overall survival in men with advanced prostate cancer, particularly those with castrate-resistant disease (2). This class of drugs includes abiraterone, apalutamide, darolutamide, and enzalutamide. Several large clinical trials have been conducted to assess the efficacy and serious adverse events of each of these medications, but the secondary quality-of-life outcomes of these studies have not been fully explored.

Objective: We aim to use quality-of-life data from existing clinical trials to determine the impact of second-generation anti-androgens on erectile and sexual function in men with advanced prostate cancer.

Study Design: We have identified 9 clinical trials on anti-androgens with data repositories available for public access. Each of these trials had patients answer questions on sexual satisfaction and erectile function using the Functional Assessment of Cancer Therapy - Prostate (FACT-P) questionnaire before and after the initiation of treatment. We will compare changes in FACT-P scores for sexual satisfaction and erectile function by type of anti-androgen as well as by anti-androgen vs. placebo. We hypothesize that second generation anti-androgens will negatively influence erectile function and sexual satisfaction scores compared to placebo.

Participants: Participants in this study include men with advanced prostate cancer who have already participated in existing clinical trials for abiraterone, apalutamide, darolutamide, or enzalutamide and have completed a FACT-P questionnaire both before and after treatment.

Main Outcome Measure: The main outcome measure is change in FACT-P questionnaire sub-score assessment of sexual function from baseline assessment to 6 month assessment.

Statistical Analysis: R Statistical software will be used for all assessments. Analysis of variance will be used to compare the average change in FACT-P sexual sub-score between different anti-androgen medications and between anti-androgen medications and placebo. Curves will be created to visually depict the change in sexual function score over time for anti-androgens and placebo. A multivariate regression will be created to identify independent predictors of sexual function preservation.

Brief Project Background and Statement of Project Significance:

Prostate cancer is the most common cancer diagnosed in men and the second most common cause of male cancer-related death (1). As PSA screening has declined in the United States, the incidence of locally advanced and metastatic prostate cancer has increased (3 - 4). In the last decade, a second generation of anti-androgen drugs have been shown to improve overall survival in men with advanced prostate cancer, particularly those with castrate-resistant disease (2). This class of drugs includes abiraterone, apalutamide, darolutamide, and enzalutamide.

The majority of these new anti-androgens function by blocking the effects of androgens such as testosterone at the cellular level (2). Due to blockade of negative feedback at the hypothalamus and pituitary gland, these medications maintain normal serum concentrations of testosterone (2). It is theorized that maintenance of normal testosterone may lead to better preservation of sexual function in these patients (5), but this theory has never been demonstrated in practice. Preservation of sexual function has long been a desire of men undergoing treatment for prostate cancer (5 - 7), and thus it is important to adequately inform men of potential sexual side-effects of treatment before initiating therapy. This project will bridge this current gap in knowledge by exploring how both erectile and sexual function are impacted in men on second-generation anti-androgens.

Specific Aims of the Project:

Aim #1: To measure how second-generation anti-androgens change the sexual function sub-score of the FACT-P questionnaire in men with advanced prostate cancer compared to each other and compared to placebo. We hypothesize that men initiated on second generation anti-androgens will experience a significant decrease in sexual function sub-score when compared to placebo.

Aim #2: To measure how second-generation anti-androgens change the sexual satisfaction sub-score and erectile function sub-score based on FACT-P questionnaire in men with advanced prostate cancer compared to each other and compared to placebo. We hypothesize that men initiated on second generation anti-androgens will experience a significant decrease in both erectile function sub-score and sexual satisfaction sub-score when compared to placebo.

Aim #3: To identify independent predictors of sexual function preservation in men with advanced prostate cancer. We predict that absence of anti-androgen therapy, absence of prior radiation therapy, absence of prior prostatectomy, and absence of prior androgen deprivation therapy will be independent predictors of preserved sexual function.

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

We have identified 9 clinical trials that tested a second generation anti-androgen in men with prostate cancer and are available by request in public repositories. Each of these trials had patients complete the Functional Assessment of Cancer Therapy - Prostate (FACT-P) questionnaire before and after treatment. We will include all patients who participated in these trials and completed the erectile function and sexual satisfaction questions in the FACT-P questionnaire before and after initiation of treatment. Patients who did not complete the sexual function questions before and after treatment will be excluded.

We will obtain data from two additional trials outside of YODA. From Clinical Study Data Request, we will obtain NCT01302041, which is a randomized controlled trial evaluating enzalutamide, and NCT02200614, which is a randomized controlled trial evaluating darolutamide. As part of our analysis, participant-level data from these outside studies will be combined with data from YODA trials to perform a meta-analysis.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

The main outcome measure is change in FACT-P questionnaire sub-score assessment of sexual function from baseline to 6 month assessment. This score is based on two questions that are answered via a five point Likert scale ranging from 0 to 4 for each question. The change in sexual function score will be calculated by subtracting the score at baseline assessment from the score at 6 month assessment, which is defined as any assessment within 5 to 7 months after treatment initiation. This value can range from -8 to +8. Changes in scores will also be measured at 1 month, 3 month, and 12 month time periods, as well as the change from initial to final assessment collected.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The independent variable will be anti-androgen drug administered, with the options being abiraterone, apalutamide, darolutamide, enzalutamide, and placebo. We will categorize this variable as the clinical trial study arm into which each patient was enrolled, staying consistent with the intention-to-treat analysis that was used in the initial study designs.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

We will examine the change in erectile function score from baseline to 6 month assessment. This score is based on the question from the FACT-P questionnaire that pertains to erectile function and is answered via a five-point Likert scale ranging from 0 to 4. The change in erectile function score will be calculated by subtracting the score at baseline assessment from the score at 6 month assessment. We will use the same methods to also examine the change in sexual satisfaction score. Other variables that we will examine include age, ECOG performance status, duration of time spent on study drug, which will be defined as the time in months on which patients received the study drug prior to final FACT-P assessment, prior cancer treatment received, which will include any treatment of prostate cancer that a patient has received prior to study enrollment, including radical prostatectomy, pelvic radiation, and androgen deprivation therapy. We will also analyze extent of disease, which will be defined as non-metastatic hormone-naive prostate cancer, metastatic hormone-naive prostate cancer, non-metastatic castrate-resistant prostate cancer, or metastatic castrate-resistant prostate cancer.

Statistical Analysis Plan:

Baseline characteristics between independent variable groups will be compared using analysis of variance (ANOVA) for continuous variables and and Kruskal-Wallis test for categorical variables. Curves will be created of change in sexual function scores over time for each independent variable category. Linear regression analysis will be done to identify any strong trends in these curves. ANOVA will be used to compare change in sexual function score between independent variable groups. A multivariate regression will be created to identify independent predictors of sexual function preservation, which will be defined as patients whose sexual function sub-score either improves, remains the same, or decreases by fewer than one point.

Software Used:

R

Project Timeline:

We anticipate having all clinical trial data in hand by September 1, 2021. Data analysis should be completed by

Novem 1, 2021. A manuscript will be drafted by January 1, 2022 and submitted for publication by March 1, 2022. We plan to report results back to the YODA Project after manuscript acceptance for publication, which we anticipate will occur by June 1, 2022.

Dissemination Plan:

Based on this research, we intend to create a manuscript with the results of our data. The manuscript will be intended for urologists and genitourinary oncologists who treat patients with prostate cancer. Potentially suitable journals for this manuscript include the Journal of Urology, European Urology, and Urologic Oncology.

Bibliography:

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